Geographic Patterns of Prostate Cancer Mortality

Evidence for a Protective Effect of Ultraviolet Radiation

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Background. **Prostate cancer is the most prevalent nonskin cancer among men in the United States and is the second leading cause of cancer deaths in men. The cause of prostate cancer remains obscure. Recently it was hypothesized that low levels of vitamin D, a hormone with potent antitumor properties, may increase the risk for clinical prostate cancer.**

Methods. **Because the major source of vitamin D is casual exposure to ultraviolet (UV) radiation, the authors examined the geographic distributions of UV radiation and prostate cancer mortality in 3073 counties of the contiguous United States using linear regression and trend surface analyses.**

Results. **The geographic distributions of UV radiation and prostate cancer mortality are correlated inversely ($P < 0.0001$). Prostate cancer mortality exhibits a significant north–south trend, with lower rates in the South. These geographic patterns are not readily explicable by other known risk factors for prostate cancer.**

Conclusions. **These data lend support to the hypothesis that UV radiation may protect against clinical prostate cancer. Viewed in conjunction with other recent data, including those demonstrating a differentiating effect of vitamin D on human prostate cancer cells, these findings suggest that vitamin D may have an important role in the natural history of prostate cancer.** ***Cancer*** **1992; 70:2861-9.**

Key words: prostate, neoplasms, geography, epidemiology, vitamin D, hormones, ultraviolet rays, calcitriol, male, human.

This article examines the geographic distribution of prostate cancer mortality in the United States to test the hypothesis that low levels of ultraviolet (UV) radiation may be associated with increased risk. An overview of prostate cancer epidemiology is followed by a description of the geographic analyses.

Prostate Cancer Epidemiology

Prostate cancer is the most commonly diagnosed nonskin cancer in men in the United States and ranks second only to lung cancer in number of cancer deaths in men.[1] In 1992, there will be approximately 132,000 incident cases and 34,000 deaths of prostate cancer.[2] Clinical prostate cancer is strongly age dependent: 80% of the cases of prostate cancer occur in men older than 65 years of age. Age-adjusted incidence rates for prostate cancer are increasing slightly in the United States, in part because of improved diagnosis, but mortality rates have remained relatively stable.[2]

Mortality resulting from prostate cancer displays striking geographic variation, with international mortality rates varying 10-fold. The highest rates occur in the United States, Canada, and Scandinavia and the lowest in Hong Kong and Japan.[3] Geographic variation is also evident within the United States, where mortality rates among white men are higher in the New England and North-Central regions.[4]

Prostate cancer exhibits significant racial variation. Incidence and mortality rates for American black men are twice those for American white men. The excess risk in black men is not attributable to differences in social class.[5] Indeed, mortality rates for American black men

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Supported by National Cancer Institute grant CA48440-01 and a Cancer Prevention Award from the Lineberger Cancer Research Center (to G.G.S.).

The authors thank Dr. Melinda Meade for her encouragement and Dr. Carl Shy for his suggestion of the death certificate case–control study.

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Accepted for publication April 15, 1992.

are the highest in the world. In contrast, African black men appear to be at a relatively low risk.[6,7]

The importance of environmental factors in clinical prostate cancer is evident from studies of migrants. For example, the mortality rate for prostate cancer among the indigenous Japanese is one-fifteenth that of white men in the United States. These rates quadruple in first and second generations of Japanese migrants to the United States.[8]

Despite the wide geographic variation in prostate cancer mortality, subclinical or "latent" prostate cancer (cancer found at autopsy for other causes) is ubiquitous among older men, regardless of race or geographic location.[9-11] This strongly suggests that the variation in prostate cancer mortality reflects the influence of environmental factors that regulate tumor growth.

Various lifestyle and endocrine factors have been suggested as risk factors for prostate cancer, but none has been implicated consistently in analytic studies.[1,12] Recently, Schwartz and Hulka proposed that low levels of vitamin (hormone) D may increase the risk for clinical prostate cancer.[13] The rationale for this hypothesis is that the known risks for clinical cancer—older age, black race, and northern latitudes—all are associated with a decreased synthesis of vitamin D. Vitamin D is synthesized in the skin after exposure to UV radiation and is converted to its active form by the liver and kidneys.[14] Thus, "vitamin" D is actually a hormone[15] and now is recognized to inhibit the proliferation and promote the differentiation of many cell types that possess its receptor.[16] ("Vitamin" is a misnomer: although vitamin D is ample in the fish-rich Japanese diet,[17,18] Western diets contain very little, despite the supplementation of foods.[14] Casual sunlight exposure is the major source of vitamin D.[19]) Thus, the vitamin D hypothesis maintains that the descriptive epidemiology of clinical prostate cancer reflects the distribution of low levels of vitamin D because vitamin D, a tumor inhibitor, retards the progression of subclinical tumors to clinical cancer. This article tests some geographic predictions of the vitamin D hypothesis.

Data and Geographic Methods

Using ecologic data at the state level, Schwartz and Hulka found that prostate cancer mortality increased significantly as UV radiation decreased.[13] The current analysis involved an examination of the vitamin D hypothesis at a much larger scale—the county.

The vitamin D hypothesis makes the following predictions:

1. Prostate cancer mortality and UV radiation should be related inversely at the county level.
2. Prostate cancer mortality should exhibit a geographic trend that is the inverse of the geographic trend of UV radiation.

Testing these predictions required data sets for prostate cancer mortality and UV radiation.

Prostate Cancer Data

Stabilized rate estimates for prostate cancer mortality in the United States, aggregated at the county level, were obtained from the Biometry Branch of the Health Effects Research Laboratory, United States Environmental Protection Agency.[20] The stabilized rate estimates were computed by a two-stage empiric Bayes procedure.[21] We used the most recent data (1970–1979) for white men in 3073 counties of the 48 coterminous states. Because the data for "nonwhite" men include ethnic groups with significantly different risks for prostate cancer (e.g., black and Oriental men), the analysis was restricted to white men.

UV Radiation Data

UV radiation is shortwave radiation (0.2–0.4 μm) in the high-energy end of the electromagnetic spectrum. Levels of UV radiation commonly are measured by Robertson-Berger meters or Eppley UV photometers[22,23] and can be estimated by various techniques.[24-29] We used two indices of UV radiation—the epidemiologic index and UV count. Briefly, the epidemiologic index estimates the quantity of received UV radiation with a formula that includes cloud cover and latitude.[27,28] The formula for the UV count includes altitude and latitude.[28,29] Complete formulae for both indices are provided in the Appendix.

Data on cloud cover were obtained from the National Climatic Data Center.[28] For each county, we used the latitude and altitude of the most populous city. Because elevation data for four towns were not available, we used the UV count for 3069 of the 3073 counties (99.9% of the total). Data for latitude and altitude were obtained from standard atlases.[30,31] Data on map coordinates were provided by the Environmental Protection Agency. These data included coordinates for all 3073 counties of the continental United States, including the counties of the contiguous states and the independent cities of Baltimore, St. Louis, Carson City, and the District of Columbia.

Scotto et al.[25] studied UV measurements for ten locations in the continental United States and found that latitude explained 68% of the variation in UV count. Including altitude or cloud cover in a multiple regression analysis increased the proportion to 92% and 91%, respectively. Thus, one might expect that the epidemiologic index and UV count would be equally effective in the estimation of UV radiation because the former uses cloud cover and latitude and the latter, altitude and latitude. However, using data for the 50 states and 10 Canadian provinces, Elwood et al.[27] found a stronger correlation between skin cancer mortality and latitude than they did with skin cancer and the epidemiologic index. For this reason, we performed a third analysis using latitude alone.

Statistical Analyses

The Pearson correlation coefficients were used to determine the strength of the relationship between prostate cancer mortality and UV radiation. For the epidemiologic index, we used all counties for which cloud cover data were available ($n = 220$).

We also used a form of spatial analysis—trend surface analysis.[32] Briefly, a "trend" refers to "any large-scale systematic changes that extend smoothly and predictably from one map-edge to the other."[33]

In trend surface analysis, a surface can be represented by the following equation:

$$z = f(x, y)$$

where z is the magnitude of some attribute (e.g., prostate cancer mortality), x and y are spatial coordinates, and f is a function defined by a polynomial equation. Least-squares regression is used to obtain the equation that best fits the original surface (e.g., the mortality rates of the 3073 counties). This equation describes the overall trend of an attribute. To map this trend, a new value for each county on the original surface is predicted by the polynomial equation. This is done by solving for z. The value of z represents the height of the new surface for a given location. Thus, z is a hypothetical rate based on location. When the values of z are known for an entire area, a contour map can be produced. The deviation of each new surface value (e.g., the hypothetical mortality rate) from its original value (the actual mortality rate) is the "residual" or "error." Thus, for any trend surface equation, the height of the new surface is equal to the trend plus the residual. A coefficient of determination, r^2, describes how well the estimated trend fits the original data, and a *P* value describes the statistical significance of the trend. In this analysis, the counties of the United States are seen as a "surface" whose height is represented by prostate cancer mortality or UV radiation.

Maps were produced with the use of SYMAP, a mapping program developed by the Harvard University Laboratory for Computer Graphics and Spatial Analysis. To map prostate cancer mortality, we used a 20% random sample of data points consisting of 615 county centroids. All 220 measurements were used to produce a trend surface map for the epidemiologic index.

Results

Results of the regression analyses between UV radiation and prostate cancer mortality are presented in Table 1. For both the epidemiologic index and UV count, the correlations with prostate cancer mortality were negative and highly significant. The strongest association was found between the epidemiologic index and prostate cancer ($r = -0.25$, $P < 0.0002$), indicating that 6% of the variation in prostate cancer mortality was "explained" by variations in UV radiation. The correlation between the UV count and prostate cancer was somewhat weaker ($r = -0.15$, $P < 0.0001$).

There was a positive correlation between latitude and prostate cancer mortality ($r = 0.19$, $P < 0.0001$). The correlation coefficient between latitude and prostate cancer mortality fell nearly halfway between those for the two indices of UV radiation.

It is of interest whether any of the three independent variables—epidemiologic index, UV count, and latitude—provides a better description of the mortality data in a linear model. In accordance with the study of Elwood et al.,[27] we examined the statistical significance between the correlation coefficients using Fisher's transformation. Latitude was a significantly better descriptor than the UV count ($P < 0.01$). The epidemiologic index was the best descriptor and was significantly better than latitude ($P < 0.01$).

Figure 1 is a choropleth map of prostate cancer mortality for the 3073 counties in the United States. This map indicates that most of the counties with low rates (i.e., 15–19 deaths per 100,000) are located in the Southeastern and East–Central states. Low rates are found throughout most of Florida, portions of southern and eastern Texas, and southern Arizona. In Arizona, the cluster of four counties with low rates stands out dra-

Table 1. Three Regression Analyses of Different Indices of Ultraviolet Radiation Exposures (Independent Variables) on Prostate Cancer Mortality (Dependent Variable) in United States Counties

Independent variable	*r*	r^2	*P*	No.
Epidemiologic index*	−0.25	0.06	0.0002	220
UV count	−0.15	0.02	0.0001	3069
Latitude†	+0.19	0.04	0.0001	3073

UV: ultraviolet.

* Significantly different from latitude ($P < 0.01$).

† Significantly different from UV count ($P < 0.01$).

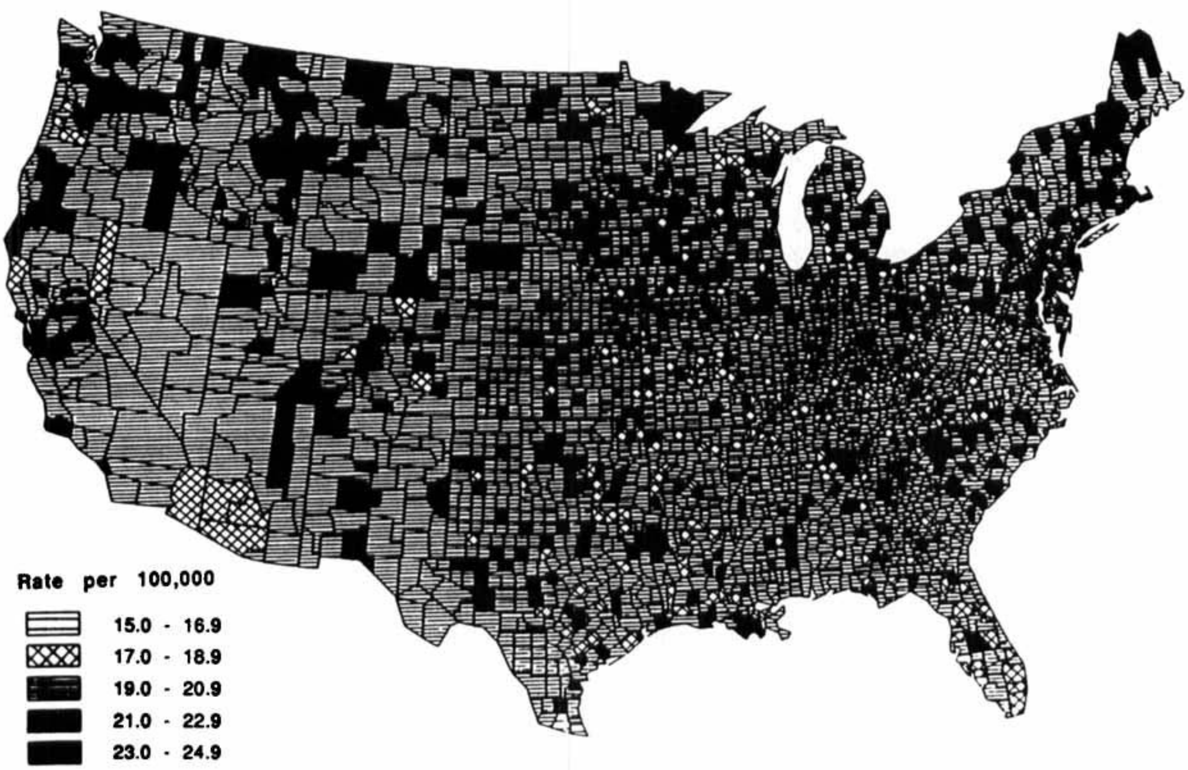

Figure 1. Prostate cancer mortality by county among white men, 1970–1979.

matically. However, the large size of these counties may exaggerate the significance of this cluster. Higher rates (21–25 deaths per 100,000) are concentrated most heavily in the northern third of the country, with additional pockets in the Midwest, California, the Intermountain West, and portions of the Carolinas. The presence of large areal units in the West exaggerates the significance of rates in these areas.

It is difficult to judge simply by visual inspection whether the map in Figure 1 depicts a north–south gradient in prostate cancer mortality. Although there are high rates in the North and low rates in the South, there is considerable "noise" throughout the country.

Linear (first-order) trend surface analysis was used to test the hypothesis of a north–south trend in prostate cancer mortality. Figure 2 shows the trend surface map. The predicted rates were divided into quartiles. Figure 2 shows a general linear trend in mortality from North to South that dips slightly to the East ($r^2 = 0.02$, $P < 0.01$). This indicates that, overall, prostate cancer mortality is highest in the Northeast (Maine and New England) and lowest in the Southwest.

Figure 3 shows the linear trend surface map of UV radiation, using the epidemiologic index ($n = 220$). Predicted rates were divided into quartiles. The highest values for the epidemiologic index are found in Florida and Texas, the lowest in Maine. The surface is tipped slightly to the East, indicating that, for a specific latitude, there is a trend for the epidemiologic index to be slightly higher in the West ($r^2 = 0.83$, $P < 0.001$).

Figure 4 shows the standardized residuals from the first-order trend surface analysis of prostate cancer mortality. Residual values for most of the surface fall within 1 standard error of the estimate. This indicates that there is a significant amount of low-level "noise" (variation) in the rate estimates that does not yield much information about local effects but detracts from the variation explained by the trend. This contributes to the low r^2 value for the first-order trend surface.

The most extreme values occur in southern Texas, where residuals lower than -2 standard error (s) are found. The highest residuals ($> +2s$) are located in central Wyoming. Large pockets of high residuals ($+1s$ to $+2s$) are located in Montana, southeastern Wyoming, west–central Missouri, and south–central New York. Residuals in this same range coincide with the location of several large cities: Chicago, Salt Lake City, Austin, San Antonio, New Orleans, Baltimore, Buffalo, Cleveland, and Providence.

Pockets of lower residuals ($-2s$ to $-1s$) are located in the Adirondacks of New York, western Vermont, northern California, western Arizona, western Colo-

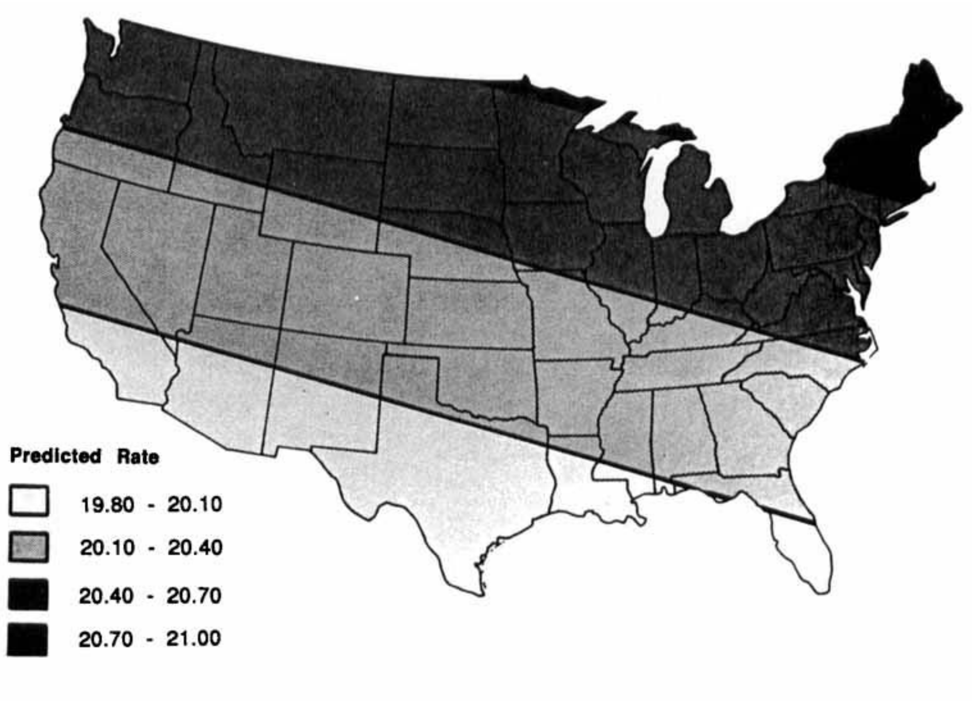

Figure 2. Linear trend surface map of prostate cancer mortality among white men, 1970–1979.

rado, the Seattle area, western Wyoming, the Minnesota–Iowa border, the "thumb" of Michigan, the Colorado–New Mexico border, portions of Oklahoma and Kansas, and Beaufort, North Carolina.

Discussion

This research examined the geographic distributions of UV radiation and prostate cancer mortality among white men in the United States. Using data from the 3073 contiguous United States counties, we found that UV radiation and prostate cancer mortality are correlated inversely. Our observations are consistent with those of a previous report and add support for the hypothesis that UV radiation may inhibit the development of clinical prostate cancer.[13]

Although highly significant statistically ($P < 0.002$), the size of the correlation between prostate cancer mortality and UV radiation, as measured by the epidemio-

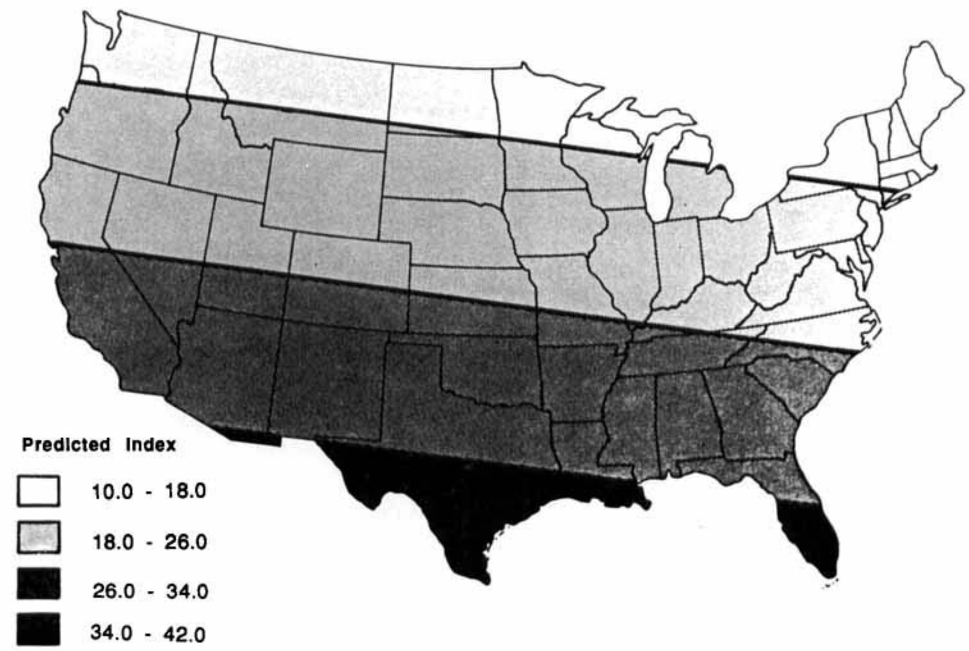

Figure 3. Linear trend surface map of UV radiation using the epidemiologic index.

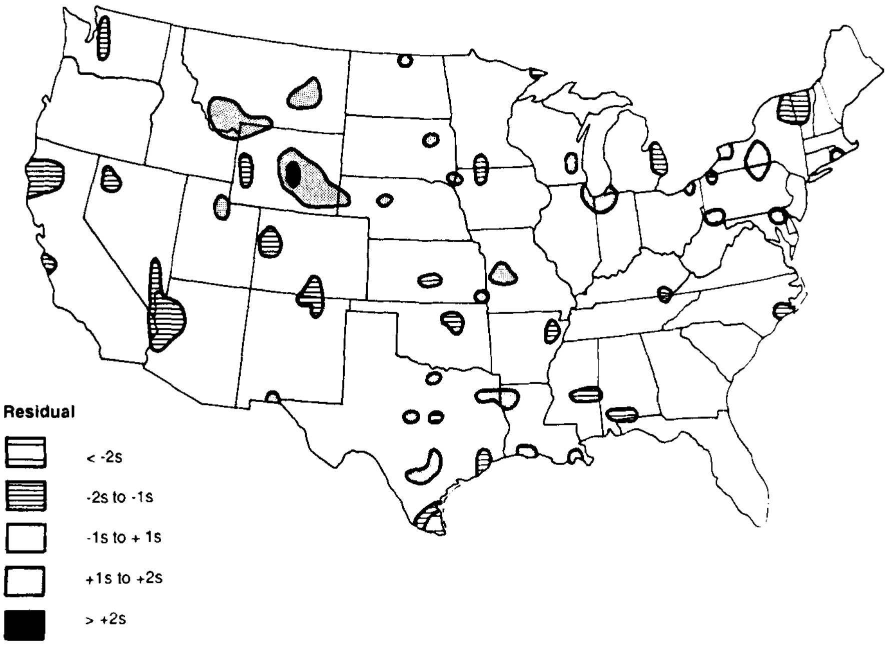

Figure 4. Standardized residuals from linear trend surface map of prostate cancer mortality among white men, 1970–1979.

logic index, was relatively modest (r = 0.25). Several factors may account for the modest size of the correlation. Most importantly, our measures of exposure were relatively crude. Many variables influence the exposure of a person to UV radiation, including the amount of time spent in the sun and type of clothing.[34] Because this was an ecologic study, we could not measure actual UV exposure. However, our exposure assessment most likely would cause us to underestimate the true correlation between UV radiation and prostate cancer mortality. Thus, we observed a substantially higher correlation with prostate cancer mortality using the epidemiologic index, which included data on cloud cover, than we did using the UV count, which did not. Future studies of risk factors for prostate cancer at the individual level might profit by the inclusion of measurements of solar exposure. One example of such measurements is the dermatologic examination of the National Health and Nutrition Examination Survey.[35] Indeed, it would be interesting to observe the male participants of that study on a follow-up basis for their subsequent mortality experience.

Using trend surface analysis, we demonstrated that prostate cancer mortality exhibits a significant north–south trend, with lower rates in the South (Fig. 2). The pattern of residuals around the linear trend is suggestive and seems to indicate higher mortality around several large cities. Because air pollution (smog) is a major factor influencing the levels of UV received at a location, residents of polluted areas may receive less UV exposure than do residents of less polluted areas.[36] This may explain the positive correlation between prostate cancer mortality and levels of particulate air pollution reported for counties in Buffalo, New York.[37] Possible explanations for areas with lower residuals are less apparent. However, many of these lower residuals are found in areas, such as western Colorado and the Adirondacks of New York, that are associated with outdoor recreation. Because we had no a priori hypotheses about the residual values, these explanations should be considered speculations. More detailed investigation of locations with unusual mortality rates may prove revealing.

It is important to consider how our findings might be influenced by bias and/or confounding factors. For example, it is conceivable that the north–south gradient in prostate cancer mortality is caused, at least in part, by improved death certification for cancer in northern states. We consider this unlikely for several reasons. First, advanced carcinoma of the prostate is not difficult to diagnose. Thus, the accuracy of death certification for prostate cancer is unlikely to vary systematically by geographic region. Moreover, were there a "diagnostic bias" of this sort, it also should appear for cancers of other anatomic sites. However, a north–south gradient is not a conspicuous feature of mortality for most nonskin cancers.[38–40] A notable exception is cancer of the colon,[41] a site for which vitamin D deficiency has been implicated in a cohort study.[42] A negative correlation between breast cancer mortality and total annual sunlight in 87 regions of the United States was reported recently by Garland et al.[43] This observation is consistent with the hypothesis that cancers of the colon, breast, and prostate may share common causes.[6,44]

It is possible that the inverse correlation between prostate cancer mortality and UV radiation is a spurious finding caused by the correlation of these variables with a third, causal factor (i.e., confounders). However, because there are few known risk factors for prostate cancer (other than age and race),[2,5] potential confounders are difficult to specify. In their study of prostate cancer mortality in the United States at the county level, Blair and Fraumeni found that rates among white men in the United States were higher in the North Central and New England states and were slightly greater in counties with higher socioeconomic levels.[4] The higher mortality rates in these regions persisted after adjustment for socioeconomic levels and other demographic factors.[4] This is consistent with the results of most epidemiologic studies, including the Third National Cancer Survey, which generally have not found associations between socioeconomic status and prostate cancer.[5,45] Thus, we conclude that it is unlikely that the inverse correlation between UV radiation and prostate cancer mortality results from confounding by socioeconomic status.

Several mortality studies have found an increased risk of prostate cancer among farmers.[46–48] Because farmers presumably receive considerable exposure to UV radiation, these findings are contrary to those expected with the vitamin D hypothesis. It is possible that farmers have unique exposures that increase their risk of prostate cancer. However, because farmers constituted approximately 6% of the total male work force in the United States between 1960 and 1970,[49] it is unlikely that confounding by farming occupation influenced our results significantly.

International correlations have suggested that diets high in fat may contribute to the development of prostate cancer.[50] It is conceivable that the intranational correlations we observed may, at least in part, reflect a higher consumption of fats by white people at more northern latitudes in the United States. The current study could not address this possibility. However, the epidemiologic index accounted for significantly more of the variation in prostate cancer mortality than did latitude. This suggests that confounding variables, if present, are associated more closely with UV radiation.

Our analyses used mortality rather than incidence rates. Because incidence reflects the number of tumors that have progressed from a latent to a clinical stage, the vitamin D hypothesis should pertain to incidence and mortality. However, although incidence data are available in only a few geographic areas (e.g., the Surveillance, Epidemiology, and End Results registries), mortality rates are available for the 3073 counties of the United States. The large size of the mortality data set permits the application of techniques, such as trend surface analysis, that can detect relatively subtle patterns, such as the north–south trend we observed.

We used measures of UV radiation as surrogate measures for exposure to vitamin D. Geographic latitude and exposure to UV radiation are well known determinants of the vitamin D status of healthy adults.[36,51–53] For example, M'Buyamba-Kabangu et al. compared the vitamin D endocrine systems of healthy black men born in Zaire with those of Zairian black people who were of similar ages and were living in Belgium. The serum levels of 25-hydroxyvitamin D, the major circulating form of vitamin D, were significantly lower in the black people living in Belgium and were correlated negatively with the duration of their European stay.[54] A similar relationship for 25-hydroxyvitamin D has been reported for Asian immigrants to the United Kingdom.[55]

In summary, this study was designed to test the hypothesis of a protective role of UV radiation on the geographic pattern of prostate cancer mortality. We found that the prostate cancer mortality in the contiguous counties of the United States is correlated inversely with UV radiation and exhibits a significant north–south trend. These findings are consistent with previous findings for black and white men at the state level and lend support to the hypothesis of a protective role of UV radiation.[13]

A plausible biologic mechanism for the inverse association between UV radiation and prostate cancer mortality involves the antitumor properties of vitamin D. It is now apparent that vitamin D plays a regulatory role in the growth of diverse normal and malignant cells (see Holick[14] and Manolagos[16] for reviews). For example, 1,25-dihydroxycholecalciferol, the hormonal form of vitamin D,[19] inhibits the replication of cells derived from breast cancer and melanoma[56,57] and prolongs the survival time of mice with human cancer xenografts.[58] The mechanism for this antitumor effect is unknown. However, phenotypic changes induced by 1,25-dihydroxycholecalciferol in human leukemia cells (HL-60) are preceded by a decrease in the expression of the c-*myc* oncogene.[59] This oncogene is amplified in many human prostate tumors.[60,61] The demonstration of intracellular receptors for 1,25-dihydroxycholecalciferol in the normal human prostate[62] strongly indicates a role for vitamin D in the growth regulation of this gland.

Recently, Miller et al.[63] demonstrated that physiologic concentrations of 1,25 vitamin D_3 promote the differentiation of human prostate carcinoma cells in culture. Other investigators have observed similar results (Schwartz GG, Bahnson RR. Unpublished data, 1992.) These findings suggest that vitamin D and its analogues may offer exciting avenues for research in prostate cancer prevention and therapy.

The vitamin D hypothesis also provides possibilities for additional geographic studies of prostate cancer. For example, a case–control study of prostate cancer deaths in a southern state (e.g., Florida) should show a risk for birthplace in a northern state (e.g., New York). If this is observed, future geographic studies may better define an age at which migration exerts a protective effect. A recent case–control study designed to test the vitamin D hypothesis[64] found that the consumption of cod liver oil—a dietary supplement rich in vitamin D—, at a young age had a protective effect. A cohort study of serum vitamin D in men with prostate cancer, which is now in progress, should shed additional light on the vitamin D hypothesis.

Appendix

The annual erythema (sunburn-producing) dose for a cloudless sky can be calculated as follows:

$$AD(L) = B/[1 + e^{(L-L_o)/L_f}]$$

where AD(L) is the annual erythema dose in effective joules/m^2 at latitude, L (in degrees).[27] The parameters B (joules/m^2), L_o (latitude), and L_f (latitude) are adjustable and were obtained by fitting the results of annual erythema doses. With the use of a worldwide ozone distribution, the best fit values for these parameters are $B = 24.1 \times 10^5$, $L_o = 30$ degrees, and $L_f = 15$ degrees.[24]

AD(L) was modified to create the "epidemiologic index," which includes the effects of cloud cover, cloud and smog thickness, ground albedo, and local ground elevation. We used an abbreviated form of this index developed by Elwood et al.[27]:

$$I = 100 \times \frac{1 - \Gamma e^{\theta} C}{1 + e^{(L-L_o)/L_f}}$$

where Γ is a constant with the value 0.056 (The parameter θ involves cloud thickness, but, because of the paucity of such data, θ is assigned a value of 0.[27]) The parameter C is the mean annual cloud cover, in tenths.

The second model we used to estimate annual UV light is the UV count. The UV count is based on measurements from UV meters in 10 locations in the United States; it estimates the quantity of received UV radiation with the following formula:

$$\text{UV count} = 3220000 - 49613.9\ (\text{latitude}) + 104.3\ (\text{Altitude})^{25}$$

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